Research Prioritization Topic Brief: Examining Effectiveness of 17-Alpha Hydroxyprogesterone Caproate Versus Other Progestogens to Reduce Risk of Subsequent Preterm Birth

Assessment of Prevention, Diagnosis and Treatment Options

PCORI Scientific Program Area:
Comparative Effectiveness Research
Addressing Disparities

Executive Summary

PCORI-proposed Comparative Research Question: What is the comparative effectiveness of 17-alpha hydroxyprogesterone caproate (17P) versus other progestogens to reduce the risk of preterm birth in women with a previous premature delivery, and is there evidence of disparities in access of care?

Brief Overview of the Topic: Babies born before 32 weeks are considered to be very preterm. 17P is an injection drug approved by the Food and Drug Administration (FDA) to prevent preterm birth in women pregnant with a single child who previously had a baby born prematurely. 17P is a progestogen which activates the progesterone receptor. Vaginal progesterone also reduces preterm birth, both in women with a prior preterm delivery and in women with a short cervix.[1-3]

Impact on Health and Populations: Preterm birth occurred in 10% of babies born in the United States in 2014. Black women and women with low socioeconomic status are more likely to have infants born prematurely.[4] Infants born prematurely are at increased risk of breathing problems, vision problems, hearing impairment, developmental delay and cerebral palsy. Babies born very preterm are at greater risk of poor outcomes. The adverse events of 17P or other progestogens for the mother and infant are not well known. We found no evidence on disparities in the use of 17P or other progestogens to prevent preterm birth.

Assessment of Current Options: Numerous health departments and health care organizations provide information sheets on preterm birth that mention the use of 17P to prevent preterm birth. 17P can be made by a compounding pharmacy or there is a pre-packaged injection that was approved by the FDA in 2011. Use of vaginal progesterone, often prescribed for women with a short cervix, is often not described in these information sources.

Likelihood of Implementation of Research Results in Practice: A great deal of information is available to patients and providers on 17P to prevent preterm birth. If new information becomes available on adverse events of 17P or other progestogens this information is likely to be incorporated into these resources for patients and providers. Similarly, any information on differences in effectiveness is likely to occur. A trial of over 1,700 women with an estimated completion of November 2018 (NCT01004029) is expected to provide new information on the efficacy and safety of 17P, although the maximum followup is 28 days after delivery.

Durability of Information: 17P was the first medication approved by the FDA for pregnancy since the 1990s. Any new information is likely to remain relevant for years to come.

Conclusion: Much previous and ongoing research examines the efficacy of 17P to prevent preterm birth compared with other progesterones. Less is known about the safety of 17P or its alternatives in women and infants. Black women and women with greater body mass index have different pharmacokinetic responses to 17P than other women, although the impact of this response on outcomes is not known. Little information is available on alternatives to 17P, differences in response to 17P or the safety of 17P in information sources available to patients.

Topic Brief 5: Examining effectiveness of 17-alpha hydroxyprogesterone caproate versus other progestogens to reduce risk of subsequent preterm birth.

1. Contributors:

Susan Hutfless, PhD. Johns Hopkins Evidence Based Practice Center
Irina Burd, MD, PhD - Johns Hopkins School of Medicine
Linda Szymanski, MD, PhD - Johns Hopkins School of Medicine
Catalina Suarez-Cuervo, MD - Johns Hopkins Evidence-Based Practice Center
Eric Bass, MD, MPH - Johns Hopkins Evidence-Based Practice Center

2. Introduction:

Babies born prior to 37 weeks of pregnancy are considered preterm. Babies born before 32 weeks are considered to be very preterm.[5] In 2014, preterm birth affected about 1 of every 10 infants born in the United States.[6] The rate of babies born preterm has increased since 2000. [7]

Risk factors for preterm birth include[4,8]

- Babies born to Black or African American women
- Previous preterm birth or family history of preterm birth
- A pregnancy that includes twins, triplets or more babies
- Problems with the uterus or cervix, including a shortened cervix
- Chronic health problems in the mother, such as obesity, high blood pressure, diabetes, and clotting disorders
- Cigarette smoking, alcohol use, or illegal drug use during pregnancy
- Infections during pregnancy including urinary tract infections, bacterial vaginosis, asymptomatic bacteriuria, chorioamnionitis, sexually transmitted infections, and HIV

The population of interest for this topic brief is women with a previous preterm birth.

There is only one FDA-approved treatment to prevent preterm birth. 17-alpha hydroxyprogesterone caproate (17P) is a drug that is injected into the muscle to prevent preterm birth in women pregnant with a single child who previously had a baby born

prematurely.[6] 17P is a progestogen which activates the progesterone receptor. Other forms of progestogen are available, but not specifically FDA-approved to prevent preterm birth. These include a compounded form of 17P and other topical or vaginal progestogens. The mechanism of action of the progestogen is the same, which is to activate the progesterone receptor. The difference between 17P and the other progestogen is the FDA-approval status (only 17P has an FDA approved product for this condition) and the route of delivery.

- The relevant medications indexed in the FDA drugs database, the route and their indications include:
  - Hydroxyprogesterone caproate
    - Makena® hydroxyprogesterone caproate injection is indicated to "reduce the risk of preterm birth in women with a singleton pregnancy who have a history of singleton spontaneous preterm birth."[9]
    - Hydroxyprogesterone caproate (generic) can be compounded in the event that the patient has an allergy to the branded formulation.[10,11] This product is indicated "in non-pregnant women: for the treatment of advanced adenocarcinoma of the uterine corpus (Stage III or IV); in the management of amenorrhea (primary and secondary) and abnormal uterine bleeding due to hormonal imbalance in the absence of organic pathology, such as submucous fibroids or uterine cancer; as a test for endogenous estrogen production and for the production of secretory endometrium and desquamation."[12]
  - Progesterone
    - Crinone® progesterone gel which is indicated for use in assisted reproductive technology and secondary amenorrhea. In January 2012 an FDA panel did not approve Crinone for an indication to prevent preterm birth in women undergoing a singleton pregnancy who have a short uterine cervical length at mid-trimester of pregnancy.
    - Endometrin® is a progesterone vaginal insert indicated to "support embryo implantation and early pregnancy by supplementation of corpus luteal function as part of an Assisted Reproductive Technology (ART) treatment program for infertile women."[13]

In a review of the literature published in 2016, the effectiveness of 17P or other progestogens was summarized as "progesterone is indicated for "short cervix" and "women with history of preterm birth.[14,15] There is no consistent benefit for the following groups: multiple gestations, those already experiencing preterm labor, or those with preterm rupture of membranes."[14] This same review noted harm for multiple gestation births and the contraindication of 17P or other progestogens during these pregnancies. The FDA label indicates the following adverse events related to 17P: injection site reactions (pain [35%], swelling [17%], pruritus [6%], nodule [5%]), urticaria (12%), pruritus (8%), nausea (6%) and diarrhea (2%).[9] However, there are no

studies of women or their children who received 17P after the perinatal period to identify the long-term effects of 17P.

Makena® is the only FDA-approved progestogen to prevent preterm birth among women who have previously had a singleton baby born preterm. This status has implications for the prescription of other formulations. The cost of branded 17P compared with the generic formulation has created controversy. 17P is indicated for weekly administration during weeks 16 through 37 of pregnancy. Makena® costs about ten times more per injection than the generic formulation.[16] The cost difference and its impact on co-pays or out of pocket costs may lead to disparities in the access to this medication among women with less income to pay for health care. 17P is administered as an injection. Some women may prefer to administer medication using a gel or vaginal insert instead of an injection. However, the other formulations of progesterone are not specifically indicated to prevent preterm birth.

Current sources of information on strategies to prevent preterm birth with 17P versus other progestogens:

Numerous health departments and health care organizations provide information sheets on preterm birth that mention the use of 17P to prevent preterm birth. Use of vaginal progesterone, often prescribed for women with a short cervix, is often not described in these information sources. Some of the many sources of information available to patients include websites of the Centers for Disease Control and Prevention,[6] state and local health departments[17,18] and other websites.[19,20] Information also is available for policymakers (including information summarized for policymakers from a group of Medicaid health plans)[21] and physicians.[7,22]

1. Symptoms and Patient-Centered Outcomes:

The most important outcome for women with a history of preterm birth is having a healthy baby. Preterm birth is the greatest contributor to infant death. Most preterm-related deaths occur among babies who were born very preterm. Infants born prematurely are at increased risk of breathing problems, vision problems, hearing impairment, developmental delay and cerebral palsy. Babies born very preterm are at greater risk of poor outcomes. The adverse events of 17P or other progestogens for the mother and infant are not well known.[23]

4. Impact/Burden of the Condition:

Preterm birth occurred in 10% of babies born in the United States in 2014. Black women and low-income or socioeconomic status are more likely to have infants born prematurely.[4]

There was no evidence identified on disparities in the use of 17P or other progestogens to prevent preterm birth. It is unknown if women at risk of disparities have equal access to 17P and other progestogens compared to women not at risk of disparities. Medicaid does cover branded and generic 17P.[24]

5. Evidence Gaps:

We searched for systematic reviews on 17P or progesterone to prevent preterm birth produced by the Agency for Healthcare Research & Quality's Evidence-based Practice Center Program and the Cochrane Collaboration. One Evidence-based Practice Center report and two Cochrane reviews were identified. A Cochrane review on combination treatments to prevent preterm birth was not included, although some of the combinations included progesterone.[25] The evidence gaps from a 2016 review are summarized to provide the most up-to-date information on gaps.

Progestogens for Prevention of Preterm Birth[23]

AHRQ Publication No. 12-EHC105-EF September 2012

Research Questions:

1. In pregnant women who are at risk for preterm birth (which is birth before 37 weeks gestational age), does progestogen treatment, compared to a placebo, usual care, or other interventions improve maternal or fetal/neonatal health outcomes, including but not limited to:

- Complications during pregnancy (e.g., chorioamnionitis, antenatal hospitalizations and intrauterine growth restriction)?
- Mode of birth and complications during birth (e.g., cesarean birth and surgical complications)?
- Prematurity?
- Postpartum and neonatal complications (e.g., maternal postpartum hemorrhage and intraventricular hemorrhage)?
- Longer term outcomes (e.g., neurodevelopmental delay and future reproductive outcomes)?

2. What is the nature and frequency of maternal and child adverse effects of progestogen treatment, including but not limited to:

- ES-2
- Complications during pregnancy (e.g. allergic reactions or development of gestational diabetes)?
- Mode of birth and complications during birth (e.g., unanticipated maternal harms)?

- Postpartum and neonatal complications (e.g., infections and sepsis)?
- Longer term outcomes?

3. How do the effectiveness, adverse effects, and safety of progestogen treatment differ based on the maternal risk factors for preterm birth, such as severity of prior preterm birth, degree of cervical shortening, order of multiple gestations, fetal fibronectin status, preterm premature rupture of membranes (PPROM), threatened preterm birth, and socioeconomic predictors of prematurity, including race/ethnicity?
4. How do the effectiveness, acceptability, adherence, adverse effects, and safety of progestogen treatment differ, based on the formulation, dose, frequency of administration, and gestational age at initiation or discontinuation of progestogen therapy?
5. How do the effectiveness, adverse effects, and safety of progestogen treatment differ based on cointerventions used to prevent preterm birth and its consequences, including antibiotics, corticosteroids, tocolysis, and surgical interventions such as cervical cerclage?
6. What are the effects of health system and provider factors, including provider knowledge and attitudes, provider specialty, cost of drug, availability of drug in formularies, and Medicaid and private payer coverage, on the utilization of progestogens for eligible at risk women?

Conclusions (taken directly from the report abstract):

Progestogens prevent preterm birth when used in singleton pregnancy in which the mother has had a prior spontaneous preterm birth or in which cervical length is short. The strength of the evidence supporting its use for these indications is moderate and low, respectively. In contrast, moderate strength of evidence suggests lack of effectiveness for multiple gestations. Evidence is insufficient for all other uses. Across indications, data are sparse to evaluate influence on near-term outcomes such as neonatal mortality and morbidities. Evidence is insufficient for understanding whether intervention has the ultimately desired outcome of preventing morbidity and promoting normal childhood development.

Evidence Gaps (taken directly from the report):

- Conducting comparative effectiveness trials that provide direct comparisons, for instance vaginal compared to intramuscular formulations, dose ranging studies to determine optimal effectiveness, and variation in timing of initiation and total treatment duration.
- The evidence about the influence of potential modifiers of effectiveness and safety is insufficient to guide care. Examples include the dose, timing, and duration of treatment; maternal characteristics (e.g., number and severity of prior preterm births, cervical length, body mass index, socioeconomic status, race and ethnicity, assisted reproduction)
- Investigating the influence of candidate modifiers like BMI.

- Considering larger-scale studies for some indications in which there is a suggestion of potential benefit but scope of prior research is limited, for instance among women with short cervix and no evidence of preterm labor.
- Improving documentation of adherence and discontinuation of treatment with attention to reasons for discontinuation.
- Expanding the repertoire of hormonal effects that are uniformly obtained as part of
- surveillance for harms, for instance further investigating relationship to gestational diabetes and to teratogenic risk in infants.
- Exploring potential to identify non-responders or responders that may contribute to likelihood of benefit from progestogens.
- Examining thresholds at which improvements in gestational age and birth weight translate to improve neonatal and childhood outcomes.
- Addressing maternal outcomes of treatment, for instance influence of hospitalization, tocolysis, and influence on risk of complications like gestational diabetes and pregnancy induced hypertension.
- Moving from surrogate outcomes closer to measures of critical health outcomes, for instance studies powered to examine neonatal survival and developmental milestones.

Prenatal administration of progesterone for preventing preterm birth in women considered to be at risk of preterm birth[26]

Editorial Group: Cochrane Pregnancy and Childbirth Group, Published Online: 31 JUL 2013, Assessed as up-to-date: 14 JAN 2013.

Objective:

"To assess the benefits and harms of progesterone administration for the prevention of preterm birth in women and their infants."

Conclusions:

Six studies of 1,453 women with a past history of spontaneous preterm birth were identified. "The use of progesterone is associated with benefits in infant health following administration in women considered to be at increased risk of preterm birth due either to a prior preterm birth.

Evidence Gaps:

"There is limited information available relating to longer-term infant and childhood outcomes, the assessment of which remains a priority.

Further trials are required to assess the optimal timing, mode of administration and dose of administration of progesterone therapy when given to women considered to be at increased risk of early birth."

Progestational agents for treating threatened or established preterm labour[27]
Editorial Group: Cochrane Pregnancy and Childbirth Group, Published Online: 31 JAN 2014, Assessed as up-to-date: 20 JAN 2014

Objective:
"To determine if the use of progestational agents is effective as a form of treatment or co-treatment for women with threatened or established preterm labour with intact membranes."
Conclusions:
"Eight studies were included in this review, involving 563 women, but only seven studies, involving 538 women, contributed data for analyses. There are some data suggesting that the use of progestational agents results in a reduction of preterm deliveries at less than 37 weeks of gestation and an increase in birthweight. The use of a progestational agent may also reduce the frequency of uterine contractions, prolong pregnancy and attenuate the shortening of cervical length. However, the analysis was limited by the relatively small number of available studies. The power of the meta-analysis was also limited by the varying types, dosages and routes of administration of progesterone.
There is insufficient evidence to advocate progestational agents as a tocolytic for women presenting with preterm labour."
Evidence Gaps:
"The effects of the intervention on neonatal mortality and various aspects of neonatal morbidity are also crucial. These outcomes were not addressed in the previous version of our review but were addressed in two studies in this review. No statistically significant difference has been shown for the group randomised to progesterone compared with placebo. However, larger studies or combined data from various studies with similar outcome measures will be needed to achieve clinically meaningful and significant implications. Inclusion of these outcomes should be considered for any future trials investigating the effect of progesterone as a treatment option for threatened or established preterm labour."

"The available studies that investigated the use of progesterone thus far did not look at the same form of progesterone. Utrogestan was the progesterone studied by Noblot 1991 and Erny 1986. Micronised natural progesterone was used in Arikan 2011. Seventeen-alpha-

hydroxyprogesterone caproate in the form of Lentogest was used in the study by Facchinetti 2007 and in the form of Proluton depot in Chawanpaiboon 2011. Seventeen-alpha-hydroxyprogesterone caproate was also used in Tan 2012. The name of the progesterone studied was not mentioned in Fuchs 1960. The dosage and the route of administration also varied in the available studies. Progesterone was administered intramuscularly in Chawanpaiboon 2011, Facchinetti 2007, Fuchs 1960 and Tan 2012. The progesterone in the study by Noblot 1991 and Erny 1986 was given orally while the progesterone in Arikan 2011 was administered via the vaginal route. This led to the more fundamental question of which would be the most effective route of administration of progesterone for tocolysis. The only study comparing different types of progesterone was conducted by Breart el al (an excluded study), who compared the efficiency of hydroxyprogesterone caproate and chlormadinone acetate for the prevention of preterm labour (Breart 1979). The authors found no significant differences between the two groups in either the length of gestation, delay between the beginning of treatment and delivery or other parameters related to prematurity. Studies comparing the routes of administration and the appropriate dosage of progesterone for tocolysis should be encouraged."

"The number of trials comparing progestational agent and placebo or another tocolytic agent is still limited. More trials are needed to allow better assessment of the efficacy of progestational agents, especially in preventing preterm deliveries with subsequent reduction in neonatal morbidity and mortality. Emphasis should also be placed on important clinical outcomes as future trials are conducted, to allow more meaningful analysis of the results."

A 2016 expert review identified the following evidence gaps:[15]

- A trial is ongoing to address the design weaknesses of a previous Phase III trial to address the question of which progestogen is best.
  - "Is there evidence of superiority between progestogens? Given its results, the phase III study by Meis et al stimulated design and execution of numerous additional large trials that tested progestogens in a variety of populations. A significant reduction in recurrent preterm birth (36.3% vs 54.9%; relative risk [RR], 0.66 [95% confidence interval (CI), 0.54–0.81]) was demonstrated with exposure to 17-OHPC in addition to fewer deliveries at <35 weeks gestation (20.6% vs 30.7%; RR, 0.67 [95% CI, 0.48–0.93]). Although this

trial demonstrated efficacy, several concerns have been identified that include an imbalance between study groups, patient selection and generalizability of its conclusions because of the higher rate of preterm birth in the placebo group compared with other prospective observational studies, and the vehicle (castor oil) for this progestogen. Despite randomization,

the women in the placebo group had a significantly higher mean number of previous preterm births (1.6 ± 0.9 vs 1.4 ± 0.7; P = 0.007) and a significantly greater percentage of these women had >1 previous preterm delivery before enrollment, (41.2% vs 27.7%; P = 0.004 by chi square based on data presented). A confirmatory phase III trial was required by the Food and Drug Administration (FDA) for its current conditional approval, given these concerns. This study has a planned enrollment of 1707 women and is intended to replicate the efficacy of 17-OHPC as a prophylactic treatment in women with a history of preterm birth. (The PROLONG Trial-clinicaltrials.gov/ct2/show/NCT01004029) This study will also better assess the safety of the drug in singleton gestations, given its planned sample size."

- "Additional trials of progestogens are needed to assess (1) the comparable efficacy between progestogens to validate the findings of Maher et al, (2) whether dosing should be increased at differing gestational ages such as the start of the third trimester to improve efficacy, and (3) safety."

- Additional information on safety of 17P is needed
- "Structural teratogenicity has not been observed with early exposure to progestogens. Mechanisms for harm related to exposure later in gestation will likely involve alteration of progesterone receptor activity. Because these receptors are located within the central nervous system of the developing fetus, functional abnormalities such as behavioral teratogenicity requires further investigation. Basic science investigations have raised plausible concerns for such developmental abnormalities particularly for the synthetic drug. However, to date, no longer term adverse harms have been identified after exposure to either of these medications, but the data are limited."

- The comparison of natural progesterone versus 17P is needed
- "To date, the actions of the FDA regarding progestogens have resulted in approval of a synthetic hormone that is indicated for a risk factor, but the parent natural hormone remains unapproved when indicated for a well-validated biomarker. Therefore, these regulatory actions may have given the impression that 17-OHPC is the superior progestogen and that a treatment strategy based on a prophylactic approach is better. However, further assessment is needed."

- "Based on present data that were derived from phase III trials and metaanalysis, natural progesterone appears to be the safer progestogen, but plausible concerns for adverse outcomes with exposure remain. Safety for an intervention in any obstetric population is more probable when natural agents are administered at doses that yield exposures within boundaries observed in human reproduction. Robust dose-response studies have yet to be performed and should be designed carefully. Also, this treatment strategy undoubtedly will be applied to other populations who are at risk for adverse events, such as women with an episode of preterm

labor. Animal data have demonstrated the potential for adverse events, which include death, when supplemental progestogens are administered in models for preterm labor."

- Biomarkers are needed to identify women at highest risk of preterm birth
  - "Defining an optimal strategy for preterm birth prevention based on a risk factor or a biomarker for a presumed pathophysiologic process (a decline in progesterone action) or both can improve the risk-benefit ratio, lower health care costs, and enhance translation of scientific findings along particular paths."
  - "In a secondary analysis derived from patients who were enrolled in the trial by Meis et al, an increased risk for preterm birth was observed in subpopulations that were discriminated by progesterone receptor genotype. Manuck et al demonstrated that particular haplotype blocks (Rs503362|rs666553 and Rs578029|rs666553) were associated with an adjusted odds ratio >10 for preterm birth <32 weeks gestation with exposure to 17-OHPC in the white/Hispanic subpopulation (adjusted odds ratio, 13.98 [95% CI, 1.27–153.32] and 16.19 [95% CI, 1.27–206.77], respectively). Differences were observed by race in this study, and further pharmacogenomic investigation of treatment response by race is needed."

6. Ongoing Research:

We searched ClinicalTrials.gov, NIH Reporter and PCORI's website to identify ongoing research.

Seventy one studies were identified in ClinicalTrials.gov related to progesterone and preterm birth. Forty were completed, terminated, withdrawn or had an unknown status, 4 were active but no longer recruiting, 15 were recruiting and 12 were not yet recruiting. All studies, including those with other risk factors for preterm labor than a previous preterm birth are summarized to understand the previous and ongoing studies related to efficacy and safety.

- Relevant completed studies
  - One publication associated with a completed study identified that the half-life of 17P is shorter in black than white women and women with a greater body mass index (BMI) than lower BMIs (NCT00099164).[28]
  - One study with an anticipated completion in 2011, directly compared 17P with vaginal progesterone but did not have results posted or links to publications (NCT00579553: Comparing IM vs. Vaginal Progesterone for Preterm Birth).
  - Of the completed studies that had an associated publication or results, 17P did not prevent preterm birth in women with cervical cerclage (NCT00830765); women carrying twins or

triplets[29] (NCT00163020; NCT00099164); or women with a short cervix (NCT00439374; NCT00331695). Fish oil supplements combined with 17P did not delay preterm birth compared with 17P alone (NCT00135902).[30] These studies compared 17P with placebo, not another form of progesterone.

- Recruiting studies
  - NCT01004029: Confirmatory Study of 17P Versus Vehicle for the Prevention of Preterm Birth in Women With a Previous Singleton Spontaneous Preterm Delivery (PROLONG). This study includes a sub-aim to examine the pharmacokinetics of the study by BMI. The estimated completion is November 2018.
  - NCT01146990: A Prospective, Noninterventional Follow-Up Study of Children Aged 23 to 25 Months, Born to Mothers Who Received Hydroxyprogesterone Caproate Injection, 250 mg/mL, or Vehicle for Prevention of Preterm Birth. The primary objective of this study is to determine whether there is a difference in developmental status at 2 years of age between children whose mothers received 17P and those who received vehicle. Gestational age will be accounted for in the analysis. The estimated completion is October 2020.
  - NCT01317225: Prevention of Preterm Labor in Patients With a Previous Episode of Threatened Preterm Labor With Progesterone is a currently recruiting study that compares 17P to placebo among women in Panama. The estimated completion date was July 2015.
  - NCT01406197: Uterine Electrical Activity Before and After Progesterone Treatment for Preterm Labor which compares vaginal, topical and injected (17P) progesterone in women currently in preterm labor. The estimated completion date is August 2016.
  - NCT01178788: Progestagens for the Tertiary Prophylaxis of Preterm Delivery which compares 17P to micronized progesterone and to control in women with a short cervix. The estimated completion date was March 2012.
  - NCT00809939: 17 Alfa Hydroxyprogesterone Caproate Versus Natural Progesterone for the Prevention of Preterm Labor is an active, not still recruiting study that compares 17P to micronized progesterone and to control in women with a short cervix. Estimated completion was in March 2012.
  - NCT01050647: Progesterone for the Management of Preterm, Premature Rupture of the Membranes: A Randomized Controlled Trial is an active, not still recruiting study that compares 17P to castor oil in women with preterm, premature rupture of membranes. The estimated completion is September 2016.
- Several studies not related to 17P aimed to examine the efficacy of vaginal progesterone versus no treatment to prevent preterm birth in twins and triplets. Several compared micronized forms of progesterone or pessaries to prevent preterm labor.

There were no studies in NIH Reporter on 17P to prevent preterm birth in humans. Three studies included 17P. One training grant aimed to examine genetic predictors of response to 17P in humans (5K23HD067224-06). One animal study aimed to develop a vaginal form of 17P and test it in rabbits (2U54HD047905-11). Another aimed to examine the neurological effects of rodents exposed to 17P in utero (5R21HD076430-02). There were no comparative studies of progestogens to prevent preterm birth.

None of these studies mentioned any specific subpopulation.

PCORI has no ongoing or previously funded work directly related to 17P.[31]

7. Likelihood of Implementation of Research Results in Practice:

Much information is available to patients and providers on 17P to prevent preterm birth. If new information becomes available on adverse events of 17P or other progestogens this information is likely to be incorporated into these resources for patients and providers. Similarly, any information on differences in effectiveness is likely to be used. A trial of over 1,700 women with an estimated completion of November 2018 (NCT01004029) is expected to provide new information on the efficacy and safety of 17P, although the maximum followup is 28 days after delivery.

8. Durability of Information:

17P was the first medication approved by the FDA for pregnancy since the 1990s. Any new information is likely to remain relevant for years to come.

9. Potential Research Questions:

- Ongoing studies are comparing 17P to other forms of progesterone. The major gap in the literature is the safety of 17P for women and infants. There is one study with an anticipated completion date in 2020 that aims to compare outcomes after 17P in infants. No studies explicitly aim to compare the safety of 17P in mothers.

- What is the short-term and long-term comparative safety of 17P versus other forms of progesterone for mothers? Does the safety vary in women with greater BMI or different races who appear to have different pharmacokinetic responses?
- When is the optimal time to initiate treatment with 17P or other progestogens during the pregnancy?

10. Conclusion:

Much previous and ongoing research examines the efficacy of 17P to prevent preterm birth compared with other progesterones. Less is known about the safety of 17P or its alternatives in women and infants. Black women and women with greater BMI have different pharmacokinetic responses to 17P than other women, although the impact of this response on outcomes is not known. There is little information on alternatives to 17P, differences in response to 17P or the safety of 17P in information sources available to patients.

APPENDIX

Methods

Literature search:

From December 2015 to February 2016, we conducted a literature review to identify evidence-based research around the effectiveness of 17P versus other progestogens to reduce risk of subsequent preterm birth. We used PubMed, Google Scholar and the Cochrane Database of Systematic Reviews to identify systematic reviews, meta-analyses and research reports and the most current reviews. We also searched the websites for government agencies, such as the CDC, the NIH and relevant professional associations such as the American Congress of

Obstetrics and Gynecologists, patient advocacy groups as likely to contain relevant material on the current prevalence and available treatment services as well as any references or sites suggested by our experts.

Clinical trials and NIH Funding Announcements:

In January 2016, we conducted a search on clinicaltrials.gov, the NIH reporter and PCORI for open clinical trials related to the topic. We used the broad search terms “preterm birth” and “progesterone”.

References for topic Examining effectiveness of 17-alpha hydroxyprogesterone caproate versus other progestogens to reduce risk of subsequent preterm birth.

1. Fonseca EB, Celik E, Parra M, Singh M, Nicolaides KH. Progesterone and the risk of preterm birth among women with a short cervix. *New Engl J Med.* Aug 2 2007;357(5):462-469.
2. Hassan SS, Romero R, Vidyadhari D, et al. Vaginal progesterone reduces the rate of preterm birth in women with a sonographic short cervix: a multicenter, randomized, double-blind, placebo-controlled trial. *Ultrasound Obstet Gynecol.* Jul 2011;38(1):18-31.

3. Romero R, Nicolaides K, Conde-Agudelo A, et al. Vaginal progesterone in women with an asymptomatic sonographic short cervix in the midtrimester decreases preterm delivery and neonatal morbidity: a systematic review and metaanalysis of individual patient data. *Am J Obstet Gynecol.* Feb 2012;206(2):124.e121-119.
4. Blencowe H, Cousens S, Chou D, et al. Born Too Soon: The global epidemiology of 15 million preterm births. *Reproductive Health.* 2013;10(Suppl 1):S2.
5. Monangi NK, Brockway HM, House M, Zhang G, Muglia LJ. The genetics of preterm birth: Progress and promise. *Semin Perinatol.* Dec 2015;39(8):574-583.
6. Centers for Disease Control and Prevention. CDC. Preterm birth. 2015; http://www.cdc.gov/reproductivehealth/maternalinfanthealth/pretermbirth.htm. Accessed February 5, 2016.
7. American Congress of Obstetricians and Gynecologists, District II. Preventing Preterm Birth- The Role of 17α Hydroxyprogesterone Caproate. 2008; ACOG Committee Opinion No. 419. Available at: http://new.dhh.louisiana.gov/assets/docs/17P/docs/ACOG_17PResourceGuide.pdf.
8. Frey HA, Klebanoff MA. The epidemiology, etiology, and costs of preterm birth. *Semin Fetal Neonatal Med.* Jan 11 2016.
9. Food and Drug Administration. FDA. Makena Prescribing Information. 2013; http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/021945s005lbl.pdf. Accessed February 21, 2016.
10. Food and Drug Administration. FDA. Hydroxyprogesterone Caproate (17P). 2014; http://www.fda.gov/drugs/guidancecomplianceregulatoryinformation/pharmacycompounding/ucm402614.htm. Accessed February 21, 2016.
11. Food and Drug Administration. FDA. Updated FDA Statement on Compounded Versions of hydroxyprogesterone caproate (the active ingredient in Makena)2012.
12. Hydroxyprogesterone Caproate Injection USP. *McGuff Pharmaceuticals, INC.*2015.
13. Food and Drug Administration. FDA. Endometrin Prescribing Information. 2008; http://www.accessdata.fda.gov/drugsatfda_docs/label/2008/022057s001lbl.pdf. Accessed February 22, 2016.
14. O'Brien JM, Lewis DF. Prevention of preterm birth with vaginal progesterone or 17-alpha-hydroxyprogesterone caproate: a critical examination of efficacy and safety. *Am J Obstet Gynecol.* Jan 2016;214(1):45-56.
15. Harrison MS, Goldenberg RL. Global burden of prematurity. *Semin Fetal Neonatal Med.* Dec 28 2015.
16. NPR. Pregnancy Woes: Why Did The Price Of My Progesterone Skyrocket? *CommonHealth* 2014.
17. Mississippi State Department of Health. Questions and Answers About 17P and Preterm Births. 2015; http://msdh.ms.gov/msdhsite/_static/41,13858,376,621.html. Accessed February 2, 2016.
18. North Carolina Public Health. Preventing Preterm Birth: Progesterone Treatment (17P) Important Information You Need to Know. 2007; Published by Noirbaby, Inc., for the 17P

Project, the NC Division of Public Health and the UNC Center for Maternal and Infant Health; http://mombaby.org/PDF/17P%20Factsheet.pdf.

19. March of Dimes. Progesterone treatment to help prevent premature birth. 2016; http://www.marchofdimes.org/complications/progesterone-treatment-to-help-prevent-premature-birth.aspx#.
20. Mayo Clinic. Preterm Labor- Treatments and drugs. 2014; http://www.mayoclinic.org/diseases-conditions/preterm-labor/basics/treatment/con-20035359.
21. Medicaid Health Plans of America - Center for Best Practices. Preterm Birth Prevention: Evidence-Based Use of Progesterone Treatment Issue Brief and Action Steps for Medicaid Health Plans, November 2014. *Medicaid Helath Plans of America - Center for Best Practices* 2014; http://www.mhpa.org/_upload/PTBIssueBrief111714MHPA.pdf.
22. United HealthCare. Updated Information about 17 Alpha-Hydroxyprogesterone Caproate (17P) Injection. 2012; https://www.unitedhealthcareonline.com/ccmcontent/ProviderII/UHC/en-US/Assets/ProviderStaticFiles/ProviderStaticFilesPdf/Clinician%20Resources/Womens%20Health/Makena_17P_Overview.pdf. Accessed February 2, 2016.
23. Likis FE, Andrews JC, Woodworth AL, Velez Edwards DR, Jerome RN, Fonnesbeck CJ, McKoy JN, Hartmann KE. Progestogens for Prevention of Preterm Birth. Comparative Effectiveness Review No. 74. (Prepared by the Vanderbilt Evidence-based Practice Center under Contract No. 290-2007-10065-I). AHRQ Publication No. 12-EHC105-EF. Rockville, MD: Agency for Healthcare Research and Quality. September 2012. www.effectivehealthcare.ahrq.gov/reports/final.cfm.
24. MomBabyOrg. Order 17P Medicaid. 2014;; http://www.mombaby.org/index.php?c=2&s=58&p=607. Accessed February 22, 2014.
25. Vogel JP, Nardin JM, Dowswell T, West HM, Oladapo OT. Combination of tocolytic agents for inhibiting preterm labour. *Cochrane Database Syst Rev.* 2014;7:Cd006169.
26. Dodd JM, Jones L, Flenady V, Cincotta R, Crowther CA. Prenatal administration of progesterone for preventing preterm birth in women considered to be at risk of preterm birth. *Cochrane Database Syst Rev.* 2013;7:Cd004947.
27. Su LL, Samuel M, Chong YS. Progestational agents for treating threatened or established preterm labour. *Cochrane Database Syst Rev.* 2014;1:Cd006770.
28. Caritis SN, Sharma S, Venkataramanan R, et al. Pharmacokinetics of 17-hydroxyprogesterone caproate in multifetal gestation. *Am J Obstet Gynecol.* Jul 2011;205(1):40.e41-48.
29. Caritis SN, Rouse DJ, Peaceman AM, et al. Prevention of preterm birth in triplets using 17 alpha-hydroxyprogesterone caproate: a randomized controlled trial. *Obstet Gynecol.* Feb 2009;113(2 Pt 1):285-292.
30. Harper M, Thom E, Klebanoff MA, et al. Omega-3 fatty acid supplementation to prevent recurrent preterm birth: a randomized controlled trial. *Obstet Gynecol.* Feb 2010;115(2 Pt 1):234-242.
31. PCORI. Reproductive and Perinatal Health. *How we select research topics* 2016; http://www.pcori.org/research-results/how-we-select-research-topics/generation-and-prioritization-topics-funding-24.